REMARKS

Prior to the present amendment, claims 26-28 and 33-35 were pending. Claims 1-20, and 29-32 were previously canceled. By the present amendment, claims 26, 27, 34, and 35 have been amended. No new matter has been added. Accordingly, claims 26-28, 33-35 remain under consideration.

An unexecuted declaration under 37 CF.R. §1.132 is being submitted herewith. An executed copy of the declaration, once received, will be submitted via supplemental response.

Statement of the Substance of the Interview

Applicants are grateful to Examiner Macauley for taking the time to discuss the application with their representative, Lauren T. Emr, on September 28, 2010 via telephone.

The interview summary mailed September 30, 2010 is accurate and complete.

Claim Amendments & Declaration Under 1.132

Claims 26, 34 and 35 have been amended to remove "urokinsae (u-PA)." Additionally, the language "…effective to reduce pain, swelling, and itching due to…" has also been removed from claims 26, 35 and 35.

During the telephone discussion with Examiner Macauley, the claim language was discussed. Examiner Macauley explained her position to be that use of the terms "effective" and "reduce" require significant clinical data. The Examiner alleges that the specification does not provide enough data with regards to effectively reducing pain, swelling and itching.

In the interest of moving the application towards allowance, Applicants have amended the claims to recite that the claimed methods effectively treat hemorrhoid disease. The specific symptoms of pain, swelling and itching have been removed. Ample support for the amendment can be found throughout the application.

In addition, a declaration under 37 C.F.R. §1.132 is being submitted along with the results of two clinical trials where the claimed methods were used to treat hospitalized patients suffering from hemorrhoid disease. The declaration and data demonstrate the effective treatment of hemorrhoid disease with the claimed methods. See Exhibits A, B and C attached hereto.

Rejection under 35 U.S.C. § 112

In the office action, claims 26-28 and 33-35 have been rejected under §112, first paragraph, as allegedly lacking enablement for the "reduction of pain, swelling and itching due to hemorrhoid disease." In addition, the Examiner asserts that there is no experimental evidence using urokinase (u-PA) to treat hemorrhoid disease.

As mentioned above, Applicants have amended the claims to remove the language "…effective to reduce pain, swelling, and itching due to…" and "u-PA."

The declaration provides the results of clinical trials (phase II and phase III) that tested the effectiveness of the claimed methods. See Exhibits B and C.

In the phase II study, three (3) groups of patients suffering from hemorrhoids were observed. Group I was given a placebo. Group II was given a placebo with sodium salicylate. Group III was given recombinant streptokinase plus salicylate. See Exhibit B.

The phase II study observed patients after 5 days of treatment. In Table 1, Group III shows 52.4% of patients had a reduction of more than 90% of the initial size of the lesion by day 5. Groups I and II had a significantly lower response. See paragraph 4 of the Declaration.

Table 2 of the phase II study shows the percent of patients that had a decrease of more than 70% in size of the initial lesions and elimination of pain and edema ("total response") on day 5. Group III showed 66.7% of patients had a total response. Groups I and II showed 36.8% and 35.0% total response, respectively. See paragraph 5 of the declaration.

In the office action, the Examiner contends that the data presented in the application doesn't compare a composition without a claimed protein (e.g. SK or t-PA), but containing the inactive ingredients sodium salicylate and/or EDTA.

In the Phase II study, one of the groups was given a placebo along with sodium salicylate. The data collected in Exhibit B clearly shows that the active ingredient, streptokinase, was the cause of the effective treatment of the hemorrhoids – not the sodium salicylate.

Furthermore, in the application as filed, the compositions tested and compared in Example 5 and Table 2 consist essentially of streptokinase (SK) or tissue-type plasminogen activator (t-PA). See paragraph 8 of the Declaration.

The phase III study compared treatment of patients suffering from hemorrhoid disease with Preparation H® and streptokinase. At the various treatment milestones, it is shown that patients treated with streptokinase showed a significant increase in treatment of their hemorrhoids over patients treated with Preparation H®. See Exhibit C. See paragraph 7 of the declaration.

Accordingly, in light of the above amendments, remarks and Declaration under §1.132, Applicants respectfully request that the §112, first paragraph, rejection be reconsidered and withdrawn.

Conclusion

In view of the foregoing amendments and remarks, entry of the amendments and favorable consideration of the claims are respectfully requested. If the examiner has any

questions or concerns regarding this amendment, she is invited to contact the undersigned at the telephone number listed below. If any fees are due or any over overpayment made in connection with this paper, please charge or credit our Deposit Account No.: 082461.

Respectfully submitted,

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LTE/aca

Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Miragaya, et al.	Examiner:	Macauley, Sheridan R
Serial No:	10/540,296	Group Art Unit:	1651
Confirmation No:	3363	Docket:	976-28 PCT/US/RCE II
Filed:	January 20, 2006	Dated:	October 12, 2010
For:	FORMULATIONS FOR THE RECTAL ADMINISTRATION OF THROMBOLYTICALLY-ACTIVE AGENTS		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system on October 12, 2010.

Anne C. Arlauskas
(Printed Name)

Signature: /Anne C. Arlauskas/

DECLARATION UNDER 37 C.F.R. §1.132

I, Ana Aguilera Barreto, do hereby declare as follows:

1. I am a co-inventor of U.S. patent application serial number 10/540,296.

2. I designed and conducted clinical trials (phase II and phase III) to test the efficacy of the methods claimed in the `296 application. See Exhibits B and C attached hereto.

3. In the phase II study, three (3) groups of patients suffering from hemorrhoids were observed. Group I was given a placebo. Group II was given a placebo with sodium salicylate. Group III was given recombinant streptokinase plus salicylate. See Exhibit B.

4. The phase II study observed patients after 5 days of treatment. In Table 1, Group III shows 52.4% of patients had a reduction of more than 90% of the initial size of the lesion by day 5. Groups I and II had a significantly lower response.

5. Table 2 of the phase II study shows the percent of patients that had a decrease of more than 70% in size of the initial lesions and elimination of pain and edema ("total response") on day 5. Group III showed 66.7% of patients had a total response. Groups I and II showed 36.8% and 35.0% total response, respectively.

6. The data collected in Exhibit B clearly shows that the active ingredient, streptokinase, was the cause of the effective treatment of the hemorrhoids.

7. The phase III study compared treatment of patients suffering from hemorrhoid disease with Preparation H® and streptokinase. At the various treatment milestones, it is shown that patients treated with streptokinase showed a significant increase in treatment of their hemorrhoids over patients treated with Preparation H®. See Exhibit C.

8. Furthermore, in the application as filed, the compositions tested and compared in Example 5 and Table 2 consist essentially of streptokinase (SK) or tissue-type plasminogen activator (t-PA).

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true. Further, I hereby declare that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States code, and that such wilful false statements may jeopardize the validity of the application of any patent issued thereon.

Respectfully submitted,

Dated: _____ Signed: _____
Ana Aguilera Barreto

Exhibit B

Clinical trial (Phase II)

This clinical study comprised three groups of patients that received:
Group I: Suppositories of 2 g containing the Placebo, composed by the excipients without sodium salicylate (19 patients).
Group II: Suppositories of 2 g containing Placebo plus sodium salicylate (20 patients).
Group III: Suppositories of 2 g containing excipients, sodium salicylate and 200 000 IU of Recombinant Streptokinase (21 patients).

Table # 1 shows the distribution of patients according to the main variable of evaluation, the Healing, defined as a reduction of more than 90% of the size of the initial lesion and without the presence of pain and edema. As it can be observed, a significant dependence is detected between the success and the treatment received, in particular because of the superiority of group III that received Recombinant Streptokinase (200 000 IU) with respect to placebo (group I), with a punctual difference estimated in 36.8% (IC 95%: 12 - 62).

Table # 1. Assortment of patients according to treatment group and the Healing of the acute hemorroidal disease at 5th day *(Main Variable).*

TREATMENT		Group I *(Placebo)*	Group II *(Placebo + Salicylate)*	Group III *(SK-200 000 UI)*	T (χ^2)
N		19	20	21	
Healing after 5 days	*Yes*	3 (15.8%)	6 (30.0%)	11 (52.4%)	0.023
	No	16 (84.2%)	14 (70.0%)	10 (47.6%)	

*It was considered **Healing** all patients with Total Response in the evaluation at 5 days, given by the complete disappearance of pain and edema, and the reduction of more than 90% of the initial size of the lesion with absence of relapse nor need of thrombectomy.*

With respect to the time of Healing, a speed of Healing significantly higher in group III (SK – 200 000 IU) is detected with respect to the rest of the groups (I: placebo and II: placebo + Salicylate), with a median estimated in 5 days, while in the rest of the groups the median is found approximately in 10 – 11 days.

Table # 2 shows the results with respect to the secondary variable at 5 days *(Total Response: decrease of more of a 70% size of the initial lesion and elimination of the pain and edema).*

At 5 days, in group III (SK 200 000 UI) there was Total Response in 66.7% of the patients treated, while in groups I and II the proportion of patients with Total Response reached 36.8% and 35.0%, respectively. In this evaluation (5^{th} day), the independence probability diminishes to 0.361, observing evidences on favor of the

difference among the groups (FB=1.769) specifically group III (SK – 200 000 IU) with respect to Placebo (median difference estimated in 29.7%) and with respect to group II that received placebo + Salicylate (median difference estimated in 32.4%).

Table # 2. Assortment of patients according to the evaluation of the response at 5 days, by treatment group.

TREATMENT		Group I	Group II	Group III	T (χ^2) melting PR + No remission
	N	19	20	21	
5 days	*TR*	7 (36.8%)	7 (35.0%)	14 (66.7%)	0.106
	PR	6 (31.6%)	9 (45.0%)	3 (14.3%)	
	No remission	6 (31.6%)	4 (20.0%)	4 (19.0%)	

The answer at the 5th day was evaluated according to the following criteria:

Total Response (TR): Complete disappearance of the pain and the edema, and reduction of more than 70% of the initial size of the lesion.

Partial Response (PR): Presence of pain but with reduction of two levels in the intensity and/or disappearance of the edema (or more than 50% reduction of the size of the lesion).

Non remission: No reduction of the pain in two levels of intensity and presence of edema and no reduction of the size of the lesion or reduction of less than 50% of the initial size.

Exhibit C

Clinical trial (Phase III)

This clinical study comprised two groups of patients that received:
Group I: Suppositories of 2 g of Preparation H (110 patients). The active ingredient in this case is phenilephrine, a vasoconstrictor.
Group II: Suppositories of 2 g containing excipients, sodium salicylate and 200 000 IU of Recombinant Streptokinase (110 patients).

Table # 1. Patients' distribution by treatment group according to the Response to the 3rd, 5th day (Principal Variable) and 10th day.

TREATMENT		Preparation H	SK 200 000 IU	P (χ^2)	FB ($P(H_0)$)
N		110	110		
3rd day	*TR*	7 (6.4%)	41 (37.3%)	**9.36e-010**	**52284449 (0.000)**
	PR	37 (33.6%)	40 (36.4%)		
	NR	66 (60.0%)	29 (26.4%)		
	Prob TR (Sk-Prep.H) >20%) / Success	0.988		**30.8 (20.7; 41.2)***	
5th day	*TR*	36 (32.7%)	83 (75.5%)	**7.35e-010**	**68018440 (0.000)**
	PR	37 (33.6%)	12 (10.9%)		
	NR	37 (33.6%)	15 (13.6%)		
	Prob TR (Sk>70%) / Success	0.903 (*P(=70%): 0.949*)			
	Prob TR (Sk-Prep.H) >20%) / Success	0.998		**42.7 (30.5; 54.2)***	
10th day	*TR*	64 (58.2%)	92 (83.6%)	**0.0001**	**297.202 (0.003)**
	PR	20 (18.2%)	7 (6.4%)		
	NR	26 (23.6%)	11 (10.0%)		
	Prob TR (Sk-Prep.H)>20%)/ Success	0.834		25.5 (13.8; 36.8)*	

*Difference Sk-PH (CI 95% for this Difference)
FB: Bayes Factor in favor of dependency; P (H_0): Probability of the hypothesis of independence among the variables.

The clinical response was evaluated at 72 hours, on the 5th day and on the 10th day after starting the treatment, according to the following criteria:

- ***Total Response***: The complete disappearance of pain and edema (or of a mild intensity), and the reduction in 70% or more of the initial size of the hemorrhoid lesion.
- ***PARTIAL response***: The presence of pain and edema but with a reduction in its intensity and a reduction of the size of the lesion of 50 - 69%.

- ***No response***: No reduction in the intensity of the pain and/or the edema, and a reduction of the hemorrhoid lesion in less than 50%.

Note: if any criterion was not fulfilled, the patient was evaluated with the following lower category.

Table # 1 shows the distribution of patients according to the main evaluation variable (Total Response on the 5th day) defined as a reduction of more than 70% of the size of the initial lesion and without the presence of pain and edema *[or of mild intensity*). It also shows the evolution with this variable on the 3rd and 10th day of the treatment.

It can be observed, in the three times considered, that a significant dependence is found between the success and the treatment received, favoring those treated with SK; the probability of surpassing 20% magnitude is greater than 0.98 on the 3rd and 5th day. On the 10th day we similarly detected the dependence between the variables, although in this case the magnitude of the difference ranged from 13.8 to 36.8 with a confidence of 95%.

The results observed on the 5th day of the treatment (main variable) made it possible to respond to the working hypothesis of the study that stated a superiority of over 20% of SK compared to PH, with a punctual difference estimated in 42.7% (IC 95%: 30.5 – 54.2); and the probability that the group treated with SK would have a success above 70% is greater than 0.90 (which formed part also of the working hypothesis).